Annals of Oncology **12**: 583–584, 2001.

Editorial

High-dose chemotherapy for ovarian cancer: Are we ready to go?

"The wise man doesn't give the right answers, he poses the right questions."
– Claude Lévi-Strauss

Sixty to seventy percent of patients with invasive epithelial ovarian cancer have chemotherapy-sensitive tumors. Nevertheless, despite excellent responses most of the tumors eventually recur and the patients die of the disease. Numerous mechanisms have been invoked to explain the emergence of drug resistance, one of them being inadequate dose intensity during the initial treatment resulting in the selection of resistant cell clones. An increase of the dose of chemotherapy is the logical consequence of this observation.

Prior to the 'taxane era' several randomized trials investigating platinum dose intensity failed to demonstrate benefit for moderate increases in chemotherapy dosage without stem cell support [1–7]. The standard regimens in these trials usually contained cisplatin at a dosage of 50 mg/m^2 or carboplatin at a projected area under the curve (AUC) of 4–6 mg/ml·min. Only the Scottish trial reported that a higher dose of cisplatin (100 mg/m^2) yielded an advantage in terms of survival [8]. This study, however, has been criticized for the unexplained poor outcome of the patients in the lower dose arm. Overall, there is still no evidence from randomized trials suggesting that an increase of the dose intensity of cisplatin beyond 25 mg/m^2/week or of carboplatin beyond an AUC of 6 mg/ml·min every three weeks is beneficial [9].

At this time, we are not aware of any randomized clinical trial that would provide support for using higher than standard doses of paclitaxel.

The paper by Ledermann et al. in this issue [10] reports on one of the largest series of patients treated with high-dose chemotherapy in ovarian cancer. Most of these patients have received high-dose chemotherapy in phase II studies or outside of a clinical trial. Health agencies seem to be prepared to finance expensive treatments outside the context of clinical research, although they are still reluctant to support the same therapies within randomized clinical trials.

The paper reveals a few weak points that are unavoidable in this type of retrospective study:

- The data come from a registry report; therefore, the selection of patients is heterogeneous, and it is very likely that only patients with a relatively favorable prognosis were selected, as in similar previous studies in breast cancer [11, 12]. Nevertheless, the treatment results in terms of recurrence-free and overall survival are very similar to those of the recently reported North American registry study [13].
- Clinical data were often unavailable: the extent of residual cancer after surgery or before beginning high-dose therapy was unknown for a relevant proportion of patients. The amount of residual tumor might have an important prognostic value as illustrated by the substantially different outcomes reported by Legros (59% DFS at five years) [14] and Stiff (less than 20% DFS at five years) [15].
- Toxicity data show a considerable percentage of procedure-related deaths (7%). Similar results have been reported by Stiff (11%) [13]; in recent years, however, mortality decreased substantially to 3% with improvements in supportive measures.

This paper clearly demonstrates that high-dose chemotherapy is feasible and reasonably safe in patients with ovarian cancer. The results in terms of survival are comparable to those in chemosensitive recurrences reported by Rose (median progression free survival nine months) using a standard dose paclitaxel/carboplatin regimen [16]. Unfortunately, the current retrospective registry analysis does not allow the definition of subgroups for which high-dose therapy is more effective than conventional therapy.

In the light of the development of high-dose chemotherapy in breast cancer, the authors of this report on the same type of treatment for ovarian cancer are to be commended for avoiding the error of drawing premature conclusions but for embarking on a randomized controlled trial comparing modern conventional chemotherapy with high-dose treatment with autologous stem cell support. Their effort merits the full support of the oncology community.

S. Aebi[1] & M. Castiglione-Gertsch[1,2]
[1]Institute of Medical Oncology, University of Bern,
[2]Swiss Institute of Applied Cancer Research,
Bern, Switzerland

References

1 Colombo N, Pittelli MR, Parma G et al. Cisplatin (P) dose intensity in advance ovarian cancer (AOC): A randomized study of conventional dose (DC) vs dose-intense (DI) cisplatin monochemotherapy. Proc Am Soc Clin Oncol 1993; 12.

2 Conte PF, Bruzzone M, Carnino F et al. High-dose versus low-dose cisplatin in combination with cyclophosphamide and epidoxorubicin in suboptimal ovarian cancer· A randomized study of the Gruppo Oncologico Nord-Ovest. J Clin Oncol 1996; 14 (2): 351–6.

3. Dittrich C, Obermair A, Kurz C et al Prospective randomized trial of cisplatin/carboplatin vs. conventional cisplatin/cyclophosphamide in epithelial ovarian cancer: First results of the impact of platinum dose intensity on patient outcome (Meeting abstract). Proc Am Soc Clin Oncol 1996; 15.

4. Gore M, Mainwaring P, A'Hern R et al. Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. J Clin Oncol 1998, 16 (7): 2426–34.

5. Jakobsen A, Bertelsen K, Andersen JE et al. Dose-effect study of carboplatin in ovarian cancer: A Danish Ovarian Cancer Group study. J Clin Oncol 1997; 15 (1): 193–8.

6. McGuire WP, Hoskins WJ, Brady MF et al. Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: A Gynecologic Oncology Group study J Clin Oncol 1995; 13 (7): 1589–99.

7 Ngan HY, Choo YC, Cheung M et al. A randomized study of high-dose versus low-dose cis-platinum combined with cyclophosphamide in the treatment of advanced ovarian cancer. Hong Kong Ovarian Carcinoma Study Group. Chemotherapy 1989; 35 (3). 221–7.

8. Kaye SB, Paul J, Cassidy J et al. Mature results of a randomized trial of two doses of cisplatin for the treatment of ovarian cancer. Scottish Gynecology Cancer Trials Group J Clin Oncol 1996; 14 (7): 2113–9.

9 Thigpen JT. Dose-intensity in ovarian carcinoma: Hold, enough? J Clin Oncol 1997; 15 (4): 1291–3.

10 Ledermann JA, Herd R, Maraninchi D et al. High-dose chemotherapy for ovarian carcinoma: Long-term results from the Solid Tumour Registry of the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2001; 12 (5): 693–9 (this issue).

11 Rahman ZU, Frye DK, Buzdar AU et al. Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer. J Clin Oncol 1997; 15 (10): 3171–7.

12. Garcia-Carbonero R, Hidalgo M, Paz-Ares L et al. Patient selection in high-dose chemotherapy trials: Relevance in high-risk breast cancer. J Clin Oncol 1997; 15 (10): 3178–84

13 Stiff PJ, Veum-Stone J, Lazarus HM et al. High-dose chemotherapy and autologous stem-cell transplantation for ovarian cancer· An autologous blood and marrow transplant registry report. Ann Intern Med 2000; 133 (7)· 504–15.

14. Legros M, Dauplat J, Fleury J et al. High-dose chemotherapy with hematopoietic rescue in patients with stage III–IV ovarian cancer: Long-term results. J Clin Oncol 1997; 15 (4): 1302–8.

15. Stiff PJ, Bayer R, Kerger C et al. High-dose chemotherapy with autologous transplantation for persistent/relapsed ovarian cancer. A multivariate analysis of survival for 100 consecutively treated patients. J Clin Oncol 1997; 15 (4): 1309–17.

16. Rose PG, Fusco N, Fluellen L, Rodriguez M. Second-line therapy with paclitaxel and carboplatin for recurrent disease following first-line therapy with paclitaxel and platinum in ovarian or peritoneal carcinoma J Clin Oncol 1998; 16 (4). 1494–7.